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㉑ Covalently labeled siloxane polymers.

㉒ Disclosed herein is a method of labeling room temperature vulcanizable silicone polymers at the "T" junction branch points by utilizing cross-linkers of the formula D-SiX₃, wherein X is a leaving group and D-is a complex organic molecule useful as a dye, fluorophore, or indicator.

COVALENTLY LABELED SILOXANE POLYMERSTechnical Field

5 The invention relates to silanol-terminated polymers which are formed from bifunctional organosilicon, and cross-linked with trifunctional silane. More specifically, it relates to siloxane polymers containing covalently bound dyes, fluorophores, or other complex organic moieties at the junction points occupied by the cross-linker.

10 Background Art

15 Organic silicone polymers are useful in a variety of applications. A group of these materials, silicone polymers formed using trifunctional silanes as cross-linkers, have multiple T-junctions. These polymers are, when properly derivatized, used as the bases for polishes, water repellent coatings for fabrics, and contact lens materials. A subset of these materials is known as RTVs (room temperature vulcanizable) polymers. (It is also possible to cross-link basic polymers formed from bifunctional silane to obtain X branches through the use of tetrafunctional silane compounds.

20 In some applications, it is desirable to include, in the polymer, materials which will serve a labeling or indicating function, or which will simply color the material as in the case of colored contact lens materials. 25 For example, U.K. Patent Application 2,132,348A discloses a method and apparatus for determining the presence of oxygen which employs a sensor material embedded in silicone resin. The resin is impermeable to quenchers other than the oxygen analyte, which interfere with the determination, and thus offers an advantage over use of the sensing material directly. Similar materials are available for the detection and quantitation of other atmospheric components such as carbon dioxide or for measurement of, for example, pH or other specific analytes.

25 The present systems which employ silicone polymer supports for the detecting or coloring material suffer from the disadvantage that the reagent is not covalently bound to the polymer and therefore is both difficult to control as to concentration and is subject to instability and leakage. One approach to solving these problems is to link the detecting or other desired material covalently to the polymer support.

30 Others have applied this general approach using different, non-silicone, polymeric backbones. For example, U.S. Patent 4,194,877 to Peterson discloses the preparation of a dye/acrylic copolymer as a pH sensor. Apparently the dye material contains sufficient unsaturation to copolymerize with the acrylamide which is the basic monomer in preparing the polymeric support. Similarly, U.S. Patent 4,468,229 discloses contact lens compositions wherein reactive dye materials are covalently bound to the monomeric starting 35 materials which are then polymerized. In this case, the resulting polymer is basically a highly substituted polyethylene backbone; that is, for example, the basic polymer is of a hydroxyalkyl ester of an unsaturated acid, most commonly hydroxyethyl methacrylate. Applicants are unaware of any general method of binding indicator reagents or other desired complex reactive materials covalently to silicone polymers.

35 Since the properties of silicone polymers are advantageous in many applications, it would be useful to 40 have available the corresponding covalently labeled materials having silicone backbones. The present invention provides such methods and materials.

Disclosure of the Invention

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The invention provides labeled silicone polymers which are resistant to leakage of the label from the matrix and which permit control of the quantity of label present. The labels may be sensing reagents, dyes, fluorophores, or other materials which provide optical properties to the polymer or which provide specific reagents for detection of analytes. The desired complex derivatives are supplied in the form of cross-linking 50 trifunctional silanes of the formula D-SiX₃, wherein D is the derivatizing dye or fluorophore, and X is a leaving group responsive to the [-Si-O-] attacking nucleophile.

Accordingly, in one aspect, the invention is directed to silicone polymers containing organic dyes or fluorophores covalently bonded to the T-junctions. A particularly preferred group of dyes and fluorophores

are the polycyclic aromatic salts of heavy metal ions. The invention in other aspects also relates to methods of preparing these derivatized polymers and to intermediates in their preparation, including compounds of the formula D-SiX₃, wherein X is a leaving group most conveniently selected from halo, acyloxy, amine, oxime and alkoxy. In still other aspects, the invention relates to methods to use the resulting derivatized polymers.

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Brief Description of the Drawings

Figure 1 is a schematic indicating the derivatization of the cross-linked silicone rubbers of the 10 invention.

Modes of Carrying Out the Invention

15 Definitions

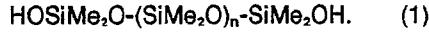
As used herein, "Complex organic moiety" refers to an organic radical which is a dye, fluorophore, or indicator for an analyte. Specifically excluded are simple alkyl and phenyl radicals, when those contain only 20 one or two functional groups which do not result in the capability of the radical to absorb or emit visible light, either when bound alone to the polymer or in the presence of a specific non-absorbing or emitting analyte, or both.

Examples of such "complex organic moieties" include acid-base indicators, such as phenolphthaleins, phenol sulfonphthaleins, aniline sulfonphthaleins, benzene, and various mixed indicators; fluorescent indicators, such as fluorescein, and chemiluminescent indicators; metal ion indicators, such as azo dyes, alizarins, 25 and triphenylmethanes; and redox indicators, such as azines, methylene blue and other thiazines, viologens, oxazines, variamine blues, indigo sulfonic acids, indophenols, indoanilines and indamines, the diphenylamine-diphenylbenzidine series, diimine iron (II) chelates, diimine ruthenium (II) chelates, diimine osmium (II) chelates, diimine iridium (III) chelates, and various mixed, fluorescent, and chemiluminescent 30 indicators. Further examples of these organic substituents include dyes for coloration, scintillators (radiation indicators) such as the POPOP's; antioxidants and oxygen scavengers, such as DABCO, BHA, BHT, and the cyclohexadienes; and indicators for specific toxic compounds, such as oxazines and certain fluorescent indicators.

"Junction" refers to the Si atom contributed by the trifunctional silane cross-linker in obtaining "T" linked silane-terminated single chain dialkyl siloxane polymers, as further described below. Thus, complex 35 organic moieties attached to the "junction" refer to those covalently bonded to this silicon.

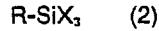
The Silicone and the Complex Organic Ligand

40 The invention is directed to a method of attaching complex organic moieties to T-junction containing silicone polymers, including room temperature vulcanizable (RTV) silicone polymers. As a class, these polymers are formed by cross-linking silanol-terminated polydialkyl siloxane, in particular, polydimethyl siloxane, with a trifunctional derivatized silane containing the complex moiety desired to be included in the finished cross-linked polymer. In general, these systems are formulated using single chain polymers of 45 molecular weight 26 kd-200 kd of the general formula conventionally written in the form of formula (1) for the most common type, the dimethyl:



For the polydimethyl siloxane polymers, the nomenclature is often abbreviated to PDM. The generic dialkyl analogs contain alkyl groups of 1-5 carbons, which are straight or branched chains. The polymers 50 which contain alkyl groups other than methyl are, however, relatively less economical and offer no particular advantage in the compositions of the invention.

To obtain the T-junction-containing forms, the single chain polymers are then cross-linked as shown in Figure 1 using a compound of the general formula



55 wherein X is a suitable leaving group and R is either methyl or a simple organic substituent such as, for example, aminoalkyl, carboxypropyl, glycidoxypropyl, phenylethylsulfonate, or vinyl. The cross-linker reacts with the PDM or other polydialkyl siloxanes by virtue of a putative nucleophilic attack on the silicon center of the cross-linker by the partially ionized hydroxy groups contained on the silanol-terminating entities in the

straight chain polymers, thus forming a series of T junctions when all three leaving groups of the R-SiX₃ cross-linker have been displaced. The mechanism of this reaction is not at present precisely understood, but it is known that the nature of X must be that of a group capable of heterolytic cleavage from Si of the form Si + :X.

5 It is evident, therefore, that the end product will contain the substituent designated "R" at the silicon atom occupying the crossbar of the T junctions brought in by the cross-linker, as illustrated in Figure 1.

In the present invention, R, rather than being a simple side chain such as methyl or the derivatives mentioned above, is a complex organic molecule such as a dye or a fluorophore which is capable of an indicating functionality. The cross-linker, therefore, has the formula

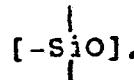
10 D-SiX₃

wherein D-can be chosen from a variety of complex substances as set forth above including heavy metal-containing sensors useful in determination of oxygen, dyes useful in coloring contact lens compositions, and fluorophores useful in tagging polymers used for various purposes to make them easy to detect.

15 Also included among the dyes and fluorophores which may be supplied according to the method of the invention are included fluorophores such as fluorescein and dansyl groups, dyes such as phenol red, methylene blue, alazarine yellow, a variety of azo dyes, and heavy metal containing dyes such as aromatic complexes of ruthenium (II), osmium (II) and iridium (III).

20 Preparation and Reaction of the Derivatized Cross-linker

The cross-linking moiety of the invention is prepared by linking the desired organic molecule to a tetrafunctional silane of the formula SiX₄ wherein X is the leaving group as set forth above, i.e., capable of displacement by the silanol end groups in PDM in the formation of a silicon oxygen bond. The general scheme is shown in Figure 1. Thus, X is generally any suitable electron withdrawing group capable of displacement by



most conveniently acyloxy. (Acyloxy is defined as a group of the formula RCOO-, wherein R is an alkyl of 1-5 carbon atoms, such as acetyl, propionyl, butanoyl, and the like).

35 Other embodiments of X may also be used. Commonly known in the art are leaving groups which are halo (particularly chloro) or an amine (particularly dimethylamino), oxime (i.e. R₂C=N-O-) or alkoxy (RO-) wherein R is alkyl as above defined. Certain of these leaving groups require a catalyst for reaction with the silanol-terminated polymer single chains; for example the reaction of alkoxy derivatized cross-linkers is catalyzed by titanates and carboxylic acid salts of zinc, iron and tin as is generally known in the art.

40 The novel cross-linking agents of the invention are therefore obtained by reaction of the compound of the formula SiX₄ with a modification of the complex organic moiety, D-, which has been modified in such manner that the organic radical D-behaves as a nucleophile. Typically such modification will take the form of a Grignard reagent containing a carbon to metal bond between D-and a metal such as lithium, magnesium, or sodium, or between a precursor of D-and such metals. Such Grignard complexes can be 45 formed using functionalities present in the dyes such as halo moieties, unsaturation, and so forth according to means generally known in the art. Of course, this reagent may also be formed with a portion of or a precursor to D-, and the complete conjugate obtained by reaction subsequent to attachment of the portion to the cross-linker, or even after the cross-linking reaction itself. Indeed, in a preferred embodiment set forth below, the diphenylphenanthroline attached to the trifunctional silane cross-linker is covalently bonded first to the silicon, and the complete 1,10-phenanthrolyl-bis (4,7-diphenyl-1,10-phenanthrolyl) ruthenium II chloride is formed using the already bound component.

50 Method of Use

55 A particularly useful series of organic dyes and photosensitizers is described in Demas, J.N., et al, J M Chem Soc (1977) 99:3547-3551, incorporated herein by reference. These compounds are generally polyphenanthroline derivatives of heavy metals. The use of these complexes in detection of oxygen is

described in the above-referenced British patent published application 2,132,348A, also incorporated herein by reference. Briefly, the fluid to be tested for oxygen is passed into contact with a silicone polymer containing the photosensitive fluorescent indicating moiety physically trapped in the matrix, but not covalently bound to it. The fluorescent light emitted by the indicating moiety under excitation is measured.

5 The oxygen contained in the test solution is capable of quenching the light emission and thus the reduction in light emission observed and measured when the matrix is in contact with the test sample is proportional to the concentration of oxygen in the test sample. The method of the invention represents an improvement over this general method in that the photosensitized sensor is covalently attached to the embedding surface and not susceptible to leakage into the solution or suspension to be assayed.

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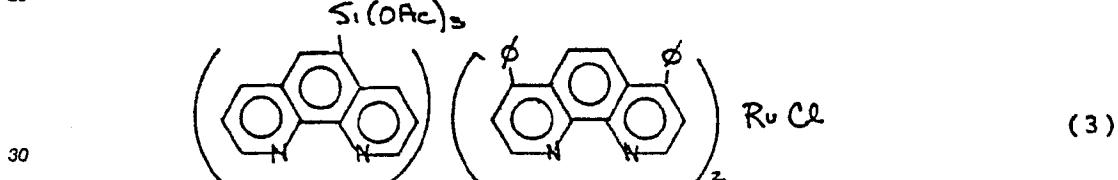
Preferred Embodiments

In one particularly preferred embodiment, a derivatized silicone rubber matrix covalently bound to a tris (phenanthroline) ruthenium (II) dye is prepared by reaction of silicon tetraacetate with 5-phenanthrolyl lithium. The resulting 5-(triacetoxysilyl)phenanthroline is then reacted with bis (diphenylphenanthroline) ruthenium (II) dichloride to obtain the desired derivatized cross-linker.

15 In more detail, 5-bromophenanthroline is reacted with n-butyl lithium to obtain the modified phenanthroline nucleus with lithium replacing bromo in the 5 position and converting the tricyclic ring system into a nucleophile. The thus modified phenanthroline is then reacted with silicon tetraacetate to obtain 5-triacetoxysilyl phenanthroline, which is then reacted in alcohol or DMF containing solvent with bis (diphenylphenanthroline) ruthenium (II) dichloride.

20 The product of the formula

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is then used as a cross-linker to form the desired polymer, carrying with it the tris diphenanthroline ruthenium moiety, 1,10-phenanthrolyl-bis (4,7-diphenyl-1,10-phenanthrolyl) ruthenium (II) chloride.

35 The cross-linker is reacted with a preparation of single chain polymeric silanol-terminated polydialkyl silane, such as with 18,000 ctsk silanol end-capped polydimethylsilane, using dibutyl tin dilaurate as a catalyst, as is generally understood in the art.

40 Examples

The following examples are intended to illustrate but not to limit the invention.

45 Example 1

Preparation of 5-Triacetoxyphenyl Phenanthroline

In a dry, oxygenless system, 0.025 g 5-bromophenanthroline is dissolved in 10 ml dry, peroxide-free tetrahydrofuran. 50 0.15 ml butyl lithium (1.6 M in toluene) solution is added with stirring. After five minutes, the contents of the reaction flask are transferred to another dry, oxygenless container in which 0.3 g silicon tetraacetate is dissolved in 10 ml dry, peroxide-free tetrahydrofuran. The silyl phenanthroline, along with the considerable excess of silicon tetraacetate, are suitable for preparation of the dye-cross-linker (Example 2).

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Example 2

Preparation of Dye-cross-linker

Samples containing 0.040 g 5-triacetoxysilyl phenanthroline and 0.08 g cis-dichloro-bis-diphenyl phenanthrolyl ruthenium (II) are combined with 10 ml 1:1 glacial acetic acid/acetic anhydride solution under 5 an inert, dry gas and stirred at 40°C for twenty-four hours.

Example 310 Preparation of Cross-linked Labeled Polymer: Polydimethylsiloxane-bound Phenanthrolyl-bis-diphenyl-phenanthrolyl Ruthenium (II)

15 5 g of silanol-capped polydimethylsiloxane, molecular weight 77,000 is dissolved in 50 ml chloroform. 0.3 grams of silicon tetraacetate or methyl triacetoxysilane containing the desired amount of dye-cross-linker of Example 2 and two drops of dibutyl tin dilaurate are rapidly beat into the chloroform solution with a blender. The solvent is then removed with a rotary evaporator. Curing is complete in a day.

Claims

20 1. A compound of the formula D-SiX₃ wherein X is a leaving group and D is a complex organic moiety.

2. A cross-linking compound of formula D-SiX₃ wherein X is a leaving group in a cross-linking reaction and D is covalently bonded to the silicon atom and is an organic moiety having a labelling or indicating function, or a precursor therefor, in the cross-linked product.

25 3. The compound of Claim 1 or 2 wherein X is selected from the group consisting of acyloxy, alkoxy, oxime, amine, and halo.

4. The compound of Claim 1, 2 or 3 wherein D is selected from an aromatic dye, a fluorophore, and an indicator moiety.

5. The compound of Claim 1, 2 or 3 wherein D is a complex containing a heavy metal.

30 6. The compound of Claim 5 wherein D is a ruthenium II complex.

7. The compound of Claim 6 wherein D is 1,10-phenanthrolyl-bis (4,7-diphenyl-1,10-phenanthrolyl) ruthenium II chloride.

8. A method of derivatizing a complex organic moiety to a silicone polymer which comprises reacting a silanol-terminated single-chain dialkyl siloxane polymer with a cross-linking compound according to any of 35 the preceding claims.

9. A silicone polymer having cross-link "T" junctions containing complex organic moieties covalently bonded at said junctions conjugated to the Si contained in the cross-linker.

10. A silicone polymer according to Claim 9, containing complex organic moieties D as specified in any of Claims 4 to 7.

40 11. A method for determining oxygen concentration in a sample which comprises exposing said sample to the polymer of Claim 9 or 10.

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